Colon cleansing before colonoscopy: Does oral sodium phosphate solution still make sense?

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Oral sodium phosphate (NaP) solution has been withdrawn from the market in the United States but remains available for over-the-counter purchase for bowel preparation for colonoscopy in Canada. The present review summarizes recent data regarding the renal toxicity of oral NaP as well as its efficacy and tolerability relative to other preparations. Given the availability of effective alternatives to NaP solution, its use for colonoscopy preparation in Canada should be limited. Candidate patients for oral NaP solution should be assessed for eligibility and preparation instructions should adhere to the current recommendations for maximizing the safety of oral NaP.

Key Words: *Bowel preparation; Colonoscopy; Sodium phosphate*

La vidange du colon avant la coloscopie : La solution de phosphate de sodium par voie orale a-t-elle encore du sens ?

La solution de phosphate de sodium (NaP) par voie orale est retirée du marché aux États-Unis mais offerte en vente libre au Canada pour les préparations intestinales de coloscopie. La présente analyse résume les données récentes au sujet de la toxicité rénale de la NaP par voie orale ainsi que de son efficacité et de sa tolérabilité par rapport à d'autres préparations. Puisqu'il existe des préparations efficaces pour remplacer la solution de NaP, il faudrait en limiter l'usage pour les préparations de coloscopie au Canada. Il faudrait évaluer les patients candidats à une solution de NaP par voie orale afin de déterminer leur admissibilité et de s'assurer que les directives de préparation respectent les recommandations actuelles afin de porter l'innocuité du NaP par voie orale au maximum.

Colon cleansing in preparation for colonoscopy continues to be a significant challenge for physicians and patients. The demand for colonoscopy continues to increase in North America and worldwide, largely in response to national colon screening programs. This demand has placed significant stress on existing colonoscopy resources. Effective colon cleansing becomes increasingly important in this environment because poor cleansing impacts the duration of the procedure and the interval recommended between procedures. The ability of the patient to tolerate the preparation is also important, because it can affect the quality of the preparation and has been identified as the most important factor underlying patient compliance in colonoscopy surveillance programs (1). Oral sodium phosphate (NaP) solution emerged in the 1990s as a popular colon cleansing agent because of favourable efficacy and patient tolerability (2-4). However, safety issues have emerged which have led to questions concerning the risk/benefit of this agent (5,6). The present article provides an overview of the qualities of an optimum colon cleansing preparation, the relative advantages and disadvantages of oral NaP solution, and the emerging trends and alternatives in colon cleansing. The present review provides a context for which the question of 'whether the use of oral NaP solution still makes sense', for bowel preparation in Canada, can be examined.

QUALITY OF THE OPTIMUM COLON CLEANSING REGIMEN

There are three fundamental components to the optimum colon cleansing preparation: cleansing efficacy, patient tolerability and safety. Cleansing efficacy affects the polyp detection rate (7,8) and duration of the procedure (9), and can influence the duration between colonoscopies in screening programs. Cleansing in the right colon is particularly important because this region presents the greatest challenge (10,11). Furthermore, there is increased recognition that flat polyps have significant premalignant potential and are preferentially found in the right colon (12,13). Patient tolerability of the preparation is also very important because it can lead to morbidity and, rarely, mortality (eg, vomiting resulting in Boerhaave's syndrome); indirectly affects the quality of the cleansing (eg, patient cannot ingest the full preparation); and is recognized to be an important determinant of compliance in colon screening programs (1). The issue of safety is magnified by the increasing number of healthy patients undergoing an elective procedure to prevent disease and by an aging population being subjected to colonoscopy. Ultimately, these factors must also be balanced against the implications of missing a clinically significant lesion (eg, flat polyp with high-grade dysplasia or carcinoma) due to poor cleansing or noncompliance due to concerns about the cleansing regimen which may result in a serious adverse outcome (eg, interval colon cancer in a screening program).

Assessment of oral NaP solution as an optimum cleansing agent

Since the original study comparing two 45 mL oral doses of NaP with 4 L of polyethylene glycol (PEG) solution almost 20 years ago (2), numerous studies have reported findings that support the original study. Two meta-analyses (14,15) of these studies (Table 1) have been conducted, which demonstrated that NaP

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provides superior colon cleansing, particularly when given in a night/morning split dosage (see split-dose regimens below), and is much better tolerated than 4 L PEG solutions. However, split-doses of PEG were typically not used in these studies.

It has been well recognized that oral NaP solution has potential safety issues because it is a small-volume osmotic agent with the ability to draw fluid from the intravascular space and cause transient hyperphosphatemia (4). However, extensive clinical trials failed to demonstrate any clinically significant sequelae resulting from these actions (4). A review in the early 2000s (4) documented that more than 2500 patients had been studied in clinical trials and there were no reports of serious adverse events. There have been a small number of case reports documenting serious adverse events; however, these appeared to be the result of inappropriate dosing and/or patient selection (eg, patients with contraindications such as renal failure or bowel obstruction). Data from the United States Food and Drug Administration (FDA) and Health Canada in early 2000 suggested the serious adverse event rate, including mortality, was similar for NaP and PEG (4). However, in 2003, a case report (16) suggested an association between chronic renal failure and nephrocalcinosis with the use of oral NaP for colon cleansing. This was followed the next year by a case series of 23 patients (5) detected from a large database of renal biopsies. The risk factors are not entirely clear, but female sex, cocomitant use of medications such as diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, underlying subclinical renal disease and the hydration status of the patient have been suggested as possible associations (5,6,17). Recent retrospective and prospective studies specifically examining the impact of NaP on renal function have not clearly identified a systematic decline in renal function (Table 2). However, of the five retrospective studies (18-22), the largest (22) reported an OR of 2.35 (doubling of serum creatinine; number needed to harm = 298). Three prospective studies (18,23,24), two of which are reported in abstract form only (23,24), have not revealed an association between the use of oral NaP and the subsequent development of renal failure. Despite these findings, small numbers of case reports suggesting an association between the use of oral NaP and renal failure continue to emerge (25,26). Most experts believe that there is an association but that the risk is low.

TABLE 1
Meta-analyses of studies comparing efficacy and tolerability of oral sodium phosphate (NaP) and polyethylene glycol (PEG)

	Hsu and Imperiale (14)	Tan and Tjandra (15)
Trials, n	8	16
Efficacy	NaP ≥ PEG (4 L)	NaP > PEG (4 L)
Tolerability	NaP > PEG	NaP > PEG

The United States FDA issued a safety alert in December 2008, stating that oral NaP for colon cleansing before colonoscopy should only be available by prescription. As a result, the CB Fleet Company (Lynchburg, USA) immediately issued a voluntary recall of their over-the-counter products for colon cleansing in the United States. The FDA's issuance followed a review after "it received more than 20 reports of a rare, but serious from of kidney failure among patients taking the drugs, known as oral phosphate products". More details can be found on the FDA Web site (www.fda.gov/medwatch/safety/2008/safety08.htm#OSP). NaP tablets remain available in the United States, but the FDA recommended that their use be restricted to appropriate candidates who are 55 years of age and younger.

To date, oral NaP solution remains available as an over-the-counter product for colonoscopy in Canada.

CURRENT TRENDS TOWARD OPTIMIZING THE USE OF ORAL NaP AND ALTERNATIVE CLEANSING REGIMENS

In the past decade, lower dose solutions, split dosing, and a mixture of sodium picosulfate, magnesium oxide and citric acid (Pico-Salax [Ferring Inc, Canada] – presently not available in United States) – have been introduced as newer strategies.

There is growing interest, particularly in the United States, in the use of lower-dose preparations of PEG, oral NaP and NaP tablets (Table 3). Low-dose PEG solution (2 L) combined with bisacodyl tablets (Halflytely [Braintree Laboratories Inc, USA] – not available in Canada) have been shown to improve

TABLE 2
Published studies examining the effects of sodium phosphate (NaP) and polyethylene glycol (PEG) on renal function

Author (reference)	Design	Primary outcome	Major finding
Abaskarhoun et al (18)	Retrospective NaP, n=600 PEG, n=150	Serum creatinine above normal range	No association with use of NaP
Brunelli et al (19)	Nested case-control; n=2237	Serum creatinine >25% from baseline or increase of >44 µmol/L	No association with use of NaP
Hurst et al (22)	Retrospective observational cohort NaP, n=6432 PEG, n=3367	≥50% increase in baseline serum creatinine NaP, n=83 PEG, n=31	1. Multivariate analysis: NaP increased risk 2. NaP OR=2.35 3. Doubling of serum creatinine: Number needed to harm = 298
Singal et al (21)	Retrospective NaP, n=157 PEG, n=154	Change in serum creatinine from baseline	NaP resulted in minor increase in serum creatinine (8.8 µmol/L) not believed by authors to be clinically significant (only reached significance when compared with PEG, which decreased serum creatinine)
Russman et al (20)	Retrospective cohort PEG, n=269 NaP, n=2083	Glomerular filtration rate <60 mL/min and decrease from baseline of >10 mL/min	No association with use of NaP

TABLE 3
Summary of 'low dose' polyethylene glycol (PEG) studies

Author (reference)	Design	Efficacy	Tolerability	Comments
DiPalma et al (27)	Bisacodyl and 2 L PEG (n=93) versus 4 L PEG (n=93)	No difference	Greater	More inadequate preparations with 2 L dose + bisacodyl
Adams et al (28)	Bisacodyl and 2 L PEG (n=191) versus 4 L PEG (n=191)	No difference	Greater	–
Johanson et al (29)	Bisacodyl and 2 L PEG (n=202) versus NaP tablets (n=200)	Less effective	Less tolerable	NaP tablets
Balaban et al (30)	Bisocodyl and 2 L PEG (n=41) versus NaP (n=80)	Less effective	No difference	Published as abstract only

NaP Oral sodium phosphate

TABLE 4
Effect of 'split dosing' of polyethylene glycol (PEG) and sodium phosphate (NaP) on efficacy

Author (reference)	Solution	Study design	Conclusion
Rostom et al (10)	NaP	Two 45 mL doses of NaP taken 6 h, 12 h or 24 h apart. 6 h doses were taken evening before the procedure; 12 h and 24 h regimens had second dose the morning of procedure	12 h or 24 h preparation most effective (ie, regimen with dose morning of procedure)
Aoun et al (34)	PEG	4 L PEG night before procedure versus 2 L PEG night before and 2 L PEG morning of procedure	Split-dose PEG was more effective, no difference in tolerability
Parra-Blanco et al (35)	PEG and NaP	Four study groups: 3 L PEG 20:00 night before procedure or 06:00 morning of procedure; 45 mL NaP 20:00 night before + 45 mL NaP 06:00 morning of procedure or 45 mL NaP 15:00 + 45 mL NaP 20:00 night before procedure	PEG or NaP with second dose given on the same day of the procedure provided the greatest efficacy

TABLE 5
Recommendations to minimize risk of adverse events with the use of oral sodium phosphate

Patient selection	Absolute contraindications	Other considerations*	
Essential to screen all patients before colonoscopy	Renal failure Congestive heart failure, ascites Significant ischemic heart disease Ileus or bowel obstruction Pregnancy Younger than 18 years of age Inability to follow instructions or ensure adequate hydration	Medications: diuretics, angiotensin-converting enzymes/angiotensin receptor blockers	
Maintain hydration	**Before colonoscopy**	**During colonoscopy**	**After colonoscopy**
	Encourage 2 L–3 L fluids over evening and up to 2 h before colonoscopy; oral rehydration solution if tolerated (eg, Gatorade [Pepsi-QTG, Canada])	Infuse saline during procedure if intravenous in place	Encourage fluids when patient leaves endoscopy suite
Proper dosing	**Dosing interval**	**Dose**	
Minimizes phosphate load and intravascular volume shift	10 h to 12 h apart; best cleansing if second dose given the morning of the procedure	45 mL/45 mL dose in Canada (do not increase dose or repeat if preparation poor)	

**See text for additional comments*

patient tolerance over the standard 4 L dose, and studies (27,28) did not detect differences in efficacy. However, the studies were not designed as equivalence trials and one study showed a significant increase in inadequate preparations in the low-dose group (27). Therefore, it remains possible that these lower volume preparations are not as efficacious. There are limited data comparing this lower volume of PEG with oral NaP (29,30) but the available data suggests less efficacy than with oral NaP (Table 3). Similarly, lower doses of oral NaP (45/30 mL – not available in Canada) are now marketed which should reduce the osmotic effect and phosphate load. Studies (31) have not detected a difference in efficacy between the low dose and standard dose but there were numerically more preparations with poorer cleansing in the lower-dose group, especially in men. Thus, there is some concern that the reduced oral NaP dose may compromise efficacy in some patients. Recent studies (32,33) examining a decreased number of NaP tablets did not detect differences in efficacy compared with standard tablet doses.

Split dosing has emerged as an important factor in cleansing efficacy and may also impact patient tolerability in large volume preparations (Table 4). This factor has become increasingly important as colonoscopy units expand their examination times from the morning to the full day. There is growing supportive data for all bowel preparations that the quality of the preparation declines considerably when the interval from the last dose exceeds 12 h, and possibly between 6 h to 12 h (10). Studies (Table 4) have shown that split dosing with NaP and PEG enhances efficacy (10,34,35).

Pico-Salax was recently introduced in Canada and has been used in the United Kingdom since 1981. In Canada, it has become increasingly popular among patients and physicians. A recent review (36) suggests this agent is better tolerated than standard regimens of NaP and PEG and has a very good safety profile (based on small studies with safety data and the paucity of serious adverse event reporting). However, the efficacy of this agent remains to be established because it is unclear whether the efficacy is similar to NaP and PEG (36).

CONCLUSIONS

The role of oral NaP solution as a colonic cleansing agent is evolving and its future is unclear. In response to recent the FDA directives, oral NaP solution is no longer available as a colon cleansing agent in the United States but it remains available in Canada as an over-the-counter product. Given the safety concerns with this agent, the recent regulatory developments in the United States, and the recent availability of alternative products in Canada, United Kingdom, Europe and Australia that better meet the criteria of an 'optimum bowel preparation' (eg, Pico-Salax with or without adjunct[s]) it is difficult to advise the continued use of oral NaP solution unless physicians and/or patients have a specific need that cannot be met by alternative products (eg, patient unable to tolerate other agents). If so, physicians and patients must be aware of its potential safety concerns and take appropriate measures to ensure that these risks are minimized. Contraindications to its use need to be strictly adhered to (Table 5) and the importance of adequate hydration stressed; oral NaP solution should be avoided in the extremes of age. NaP tablets are not available in Canada, and in the Unites States, the FDA has recommended that the use of prescription NaP tablets be restricted to low-risk patients (ie, younger than 55 years of age). Prescription use of tablets should follow practices outlined for NaP solution (Table 5).

CONFLICTS OF INTEREST: SV has served on the speaker bureau and advisory board for the CB Fleet Company and Ferring USA. He has received unrestricted educational grants from Pharma Science Canada, CB Fleet Company and Ferring Canada. He holds a patent on oral rehydration solutions and colon cleansing. DR has served on the advisory board and has received research support from the CB Fleet Company and Salix Pharmaceuticals.

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